REMARKS

Status of the Claims

Applicants note that claims 7, 9, 10, 12, 19-22, 27-30, 41, 42, 45, 46, 49, 50, 53-56, 59-67, 75-81, 85, 87, 95, and 97 are withdrawn from consideration in light of Applicants' species election and will be considered should one or more generic claims be deemed allowable, as set forth in 37 C.F.R. § 1.141. New claims 103-108 have been added as described elsewhere. Support for these new claims can be found in the specification as is described below. Therefore, no new matter has been added by way of amendment or presentation of new claims. Claims 1-108 are now pending.

The Examiner's comments are addressed below in the order set forth in the Office Action.

The Rejections of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 1-6, 8, 11, 13-18, 23-26, 31-40, 43, 44, 47, 48, 51, 52, 57, 58, 68-74, 82-84, 86, 88-94, 96, and 98-102 stand rejected under 35 U.S.C. § 103 over U.S. Patent No. 5,004,605 (Hershenson *et al.*) in view of *Merck Index* (1989), p. 859, col. 2. This rejection is respectfully traversed.

The Office Action asserts that Hershenson *et al.* teaches Applicants' claimed subject matter, except for the use of aspartic acid as a buffer. To establish a *prima facie* case of obviousness (1) there must be some suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP § 2143. *See In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991) (teaching or suggestion to make and reasonable expectation of success must be found in prior art); *In re Royka*, 49 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974)(all limitations must be taught). As will be demonstrated, the present rejection fails to establish each of the elements of a *prima facie* case.

The primary reference does not teach or suggest Applicants' claim limitations.

In the present case, independent claims 1, 36, 61, 68, 75, and 92 are directed to compositions and methods that recite the claim limitation "comprising substantially monomeric interferon-beta." The term "substantially monomeric" is defined in the specification, for example at page 7, lines 15-21. Claim 82 has been amended to recite "wherein said interferon-beta (IFN-β) or biologically active variant thereof within said composition is substantially monomeric." Support for the amendment can be found in the specification, for example, at page 7, lines 3-21. In contrast, Hershenson *et al.* does not teach or suggest compositions or methods drawn to substantially monomeric IFN-β and the rejection must be withdrawn accordingly. This is explained more fully in the following paragraphs.

> Applicants have defined "substantially monomeric" within the specification as follows.
>
> By "substantially monomeric" is intended that the majority of IFN-β (by weight) present in the composition is in its monomeric form rather than an aggregated form. By "aggregated" is intended a physical interaction between the polypeptide molecules that results in the formation of multimers (dimers, trimers, etc.) that may remain soluble or that may precipitate out of solution. The monomeric form of the IFN-β polypeptide remains soluble, and hence is said to be "solubilized" in the low-ionic-strength formulation or pharmaceutical compositions of the present invention. The percentage (by weight) of IFN-β that is in its monomeric form in the HSA-free compositions of the invention may vary from 80% or greater.

See the specification, page 7, lines 8-16.

Applicants' disclosure teaches that *soluble* aggregates of oligomeric IFN-β can be present in pharmaceutical formulations of IFN-β and that to distinguish between soluble aggregates and the molecular form of IFN-β, analytical ultracentrifugation can be utilized:

> Determination of both soluble and insoluble aggregates during storage in liquid formulations can be achieved, for example, using analytical ultracentrifugation as noted in the Examples below to distinguish between that portion of the soluble polypeptide that is present as soluble aggregates and that portion that is present in the nonaggregate, biologically active molecular form.

See the specification, page 14, lines 16-21. Applicants' disclosure explains the technique in greater detail in Example 2:

> While solubility experiments can determine how much IFN-β-1b is in solution, other techniques are required to determine the aggregation state of the protein. It is important to determine whether a protein is monomeric in a given formulation and to determine how much of the protein (if any) exists in higher ordered forms such as dimers, trimers, etc. Analytical ultracentrifugation is one of the most powerful techniques for elucidating the aggregation state of proteins (see Liu and Shire (1999) *J. Pharm. Sci.* 88:1237-1241).

See the specification, page 29, lines 2-8.

Applicants utilized analytical ultracentrifugation to confirm that their formulation maintains "substantially monomeric" IFN- β:

> Three experiments were conducted to characterize the monomeric content of several IFN-β-1b formulations with the use of analytical ultracentrifugation. These analytical ultracentrifugation experiments were each conducted with a different preparation of IFN-β-1b.

See the specification, page 29, lines 8-11. The results are set forth in Figures 3-11. For example, Figure 3 of the specification shows a formulation comprising 89.8% monomeric IFN-β.

Hershenson *et al.* does teach that their formulation contains mainly *soluble* IFN-β. See Hershenson *et al.*, column 19, lines 17-40. However, Hershenson *et al.* does not disclose that portion of the soluble polypeptide that is present as aggregates and that portion that is present as monomeric IFN-β. In particular, Hershenson *et al.* does not teach or suggest a substantially monomeric IFN-β formulation. On this basis alone, it is clear that the Office Action has not demonstrated that Hershenson *et al.* teaches or suggests all of the elements of Applicants' claims.

The primary reference does not suggest its modification or a reasonable chance of success.

Hershenson *et al.* teach and claim "a therapeutically effective amount of a recombinant interferon-β protein dissolved in an inert carrier medium comprising as a stabilizer/solubilizer an effective amount either of glycerol or of polyethylene glycol polymers having an average molecular weight from about 190 to about 1600 daltons." See, for example, column 4, lines 42-48 of Hershenson *et al.* Hershenson *et al.* explain that "[t]he pharmaceutical compositions of this invention provide a means of maintaining recombinant IFN-β in soluble form and thereby stabilizing it by use of one or more solubilizer/stabilizers of this invention." Column 6, lines 65-

68. Hershenson thus requires the use of one or more solubilizers/stabilizers to maintain a solubilized interferon formulation.

In contrast, Applicants' claims are direct to compositions and methods that recite "substantially monomeric" interferon-beta in a low-ionic-strength formulation without the use of solubilizers and/or stabilizers, such as polyethylene glycol. Hershenson *et al.* does not teach or suggest maintaining recombinant IFN-β in its substantially monomeric soluble form and thereby stabilizing it *without* one or more solubilizer/stabilizers disclosed in the cited art. Consequently, the Office Action has not demonstrated that Hershenson *et al.* suggests its modification to produce the compositions or methods recited in Applicants' claims. To the contrary, the Hershenson *et al.* reference teaches away from Applicants' claimed invention by requiring use of "solubilizer/stabilizers" to prepare soluble formulations of interferon. Further, the Office Action has not demonstrated that the teachings of Hershenson *et al.* would provide a reasonable expectation of successfully maintaining recombinant IFN-β in its substantially monomeric soluble form utilizing Applicants' low-ionic-strength formulation.

The secondary reference does not satisfy the deficiencies of the primary reference.

The Office Action also cites to Budavari, ed. (1989) *The Merck Index* (11th edition, Merck & Co., Inc., Rahway, N.J.), page 859, column 2. This secondary reference merely teaches the chemical properties of aspartic acid. (Applicants note that only page 132 has been sent with the Office Action, but that the entry for aspartic acid does appear in column 2 on this page.) It does not suggest its modification or combination with Hershenson *et al.* to produce the compositions or methods of Applicants' claimed invention. Nor does it provide a reasonable expectation of successfully maintaining recombinant IFN-β in soluble form utilizing Applicants' low-ionic-strength formulation. Finally, it does not teach or suggest use of aspartic acid to maintain substantially monomeric IFN- β formulations. Thus, it does not satisfy the deficiencies of the primary reference.

For all of these reasons, the Office Action has not demonstrated (1) a suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) a reasonable expectation of success; or (3) that the prior

art references, alone or in combination, teach or suggest all the claim limitations. None of the elements of a *prima facie* case of obviousness have been met. Accordingly, Applicants respectfully submit that this rejection of claims 1-6, 8, 11, 13-18, 23-26, 31-40, 43, 44, 47, 48, 51, 52, 57, 58, 68-74, 82-84, 86, 88-94, 96, and 98-102 should be withdrawn.

Further, the rejection should not be applied to the new claims. New claims 103 and 104 recite "...wherein said aspartic acid is present at a concentration of about 2 mM." Support for these claims can be found in the original claims and the specification at page 6, line 10. New claims 105 and 107 recite "...wherein said IFN-β is stabilized for at least 2 months at a temperature of 5°C"; new claims 106 and 108 recite "...wherein said IFN-β is stabilized for at least 2 months at a temperature of 30°C." Support for these new claims can be found throughout Examples 5, 6, 7, and 9, as well as in Figures 17, 19, 21, and 23. Each of the new claims ultimately depend from one of the independent claims. As set forth above, the Office Action has not shown a *prima facie* case of obviousness with respect to the independent claims.

In addition, new claims 105-108 recite "...wherein said IFN-β is stabilized for at least 2 months." Applicants' disclosure teaches that "[b]y 'stabilized' is intended the compositions retain the IFN-β polypeptide in its substantially monomeric state during storage, and hence the therapeutic effectiveness of this polypeptide is not compromised due to aggregate formation." See the specification, page 13, lines 23-25. Applicants' data demonstrate that the percent of the IFN-β polypeptide found within the reverse phase (RP) HPLC main peak remains constant (the main peak represents monomeric IFN-β; see Example 2 and Figures 3-5). In other words, the data show that the compositions retain the IFN-β polypeptide in its substantially monomeric state during a two-month storage, i.e., that the IFN-β polypeptide is stabilized during a two-month storage. There is no demonstration in the present rejection that Hershenson *et al.* teaches or suggests IFN-β "stabilized for at least 2 months." Accordingly, the present rejection should not be applied to new claims 105-108.

Claims 1-6, 8, 11, 13-18, 23-26, 31-40, 43, 44, 47, 48, 51, 52, 57, 58, 68-74, 82-84, 86, 88-94, 96, and 98-102 also stand rejected under 35 U.S.C. § 103 over U.S. Patent No. 5,004,605 (Hershenson *et al.*) in view of U.S. Patent No. 6,525,102 to Chen *et al.* This rejection is respectfully traversed.

Applicants thank the Examiner for noting that the reference to Chen *et al.* is cited under Sections 102(e)/103 and may be removed by making a statement as set forth in MPEP § 706.02(l)(1) and (2). Accordingly, Applicants' representative duly states:

> Upon information and belief, Applicants' representative states that the application and the reference were, at the time the invention was made, owned by, or subject to an obligation of assignment to, the same person.

Accordingly, Chen *et al.* cannot be cited. As explained in the preceding pages, the rejection based upon Hershenson *et al.* does not meet the standard for a *prima facie* case of obviousness. Consequently, Applicants respectfully submit that the present rejection must be withdrawn.

CONCLUSION

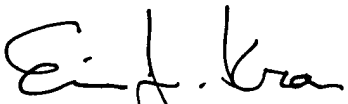
In view of the aforementioned amendments and remarks, Applicants respectfully submit that the objection to the specification and the rejections of the claims under 35 U.S.C. § 103 are overcome and that the new claims are patentable over the art cited by the Examiner. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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